https://doi.org/10.1038/s41591-023-02752-3

Emerging opportunities for gene editing therapies in India

India's population recently surpassed China's, making healthcare a crucial issue for the coming decade. Genetic diseases such as sickle cell anemia, β-thalassemia and retinal dystrophies are prevalent in India due to consanguinity and founder effects[1–3]. Therapies such as CRISPR-based gene editing need to be available in India, to reduce the dependence on costly imported drugs.

In India, healthcare is mainly community based[4], and there is little awareness of rare genetic diseases, although this has recently improved. The pandemic demonstrated India's ability to scale up the production of biologicals such as vaccines, and there is now governmental and non-governmental support for gene and cell therapy programs, including the Sickle Cell Gene Editing mission, the development of chimeric antigen receptor (CAR)-T cell therapy and indigenous vaccine development[5]. We are approaching a critical inflection point for gene editing technologies in India driven by the convergence of three critical factors: patient awareness; evolution of indigenous technologies; and availability of regulatory approval pathways.

The Sickle Cell Gene Editing mission is defining a framework for integrating administrative, research and clinical protocols to develop cutting-edge therapies in India. The Council for Scientific and Industrial Research (CSIR), the Department of Biotechnology (DBT), the Indian Council for Medical Research (ICMR) and other government agencies have funded researchers (including the authors) at the Institute of Genomics and Integrative Biology in New Delhi, GROW Labs at the Narayana Nethralaya Foundation in Bangalore, the All India Institute of Medical Sciences in New Delhi and other locations to develop indigenous gene editing and delivery strategies that can be translated to a therapy.

Indian gene editing tools and associated technologies focus on diseases that predominantly affect the disadvantaged, tribal population of the country[6]. This research, including that for sickle cell disease, has now reached the preclinical phase, with a small clinical trial to be supported by the Ministry of Tribal Affairs. In the near future, we hope to involve the biopharma industry to scale up vector production. Similar programs focusing on hemophilia and hemoglobinopathies have also been initiated at Christian Medical College in Vellore.

The use of adeno-associated virus (AAV) vectors in gene therapy has recently gained momentum in India for blood disorders, muscular dystrophies and ocular diseases. AAV vectors of different serotypes have also been produced and successfully tested in preclinical disease models using various routes of administration[7]. To translate preclinical research into human trials, the Narayana Nethralaya Foundation has recently developed Current Good Manufacturing Practices (cGMP) facilities using indigenous production processes for clinical-grade AAV vector production. Several scientific research organizations, such as the Institute of Genomics and Integrative Biology and the Indian Institute of Technology Bombay, among others, have unveiled plans for similar GMP facilities, as have some biopharma companies. Many of these organizations are licensing vector technology from academic institutions and collaborating to develop efficient vector production platforms. The academia–industry collaboration is also being fostered by the National Biopharma Mission, Department of Biotechnology and Biotechnology Industry Research Assistance Council, which is providing funding for independent research groups, start-ups and pharma. Gene therapy trials for spinal muscular atrophy and retinal dystrophies are beginning in India, with regulatory processes initiated for international products.

Innovation is needed for clinical delivery and patient access. In the case of sickle cell anemia, most of the affected population resides in economically disadvantaged tribal belts in India. CRISPR-based ex vivo gene therapies, although successfully validated in the West, would be unaffordable to people in India based on existing prices. Costs in India can be reduced through indigenous, large-scale manufacture of gene editing components and cell therapy reagents in regional GMP hubs alongside pipelines for in vivo correction supported by hematologists in local hospitals.

Patient support and advocacy organizations have raised awareness and pushed for legislative support of gene therapies in India[8]. Comprehensive patient registries have influenced policymakers, driving the development of India's nascent Rare Disease Policies. This, in turn, is driving the genetic testing and counselling services sector in India, which is a prerequisite for gene therapy. India has now published the National Guidelines for Gene and Cell Therapies, which allow organized clinical trials to be conducted in accordance with international best practice[8]. We and other researchers are working with patient foundations, which are pushing for *n*-of-1 trials of rare diseases through gene editing or gene augmentation approaches, including for neuroencephalopathies and muscular dystrophies. For example, the Institute of Genomics and Integrative Biology and GROW Labs are attempting to treat an ultra-rare neuroserpinopathy using a novel dual-AAV-delivered CRISPR base editor that corrects the mutated base without substantial off-target modifications. Possible bottleneck in *n*-of-1 trials are the lack of appropriate animal models, which hinders the rapid development of such therapies, as well as regulatory process requirements that would require reorientation for such trials.

While India consolidates local resources to manufacture gene and cell therapies at lower costs, the greatest challenge lies in wading through the complex landscape of licensing for technologies such as CRISPR–Cas9-based editing, where most of the intellectual property originates outside of India[9]. Although opportunities for commercialization do exist, it is imperative that in the coming years, sufficient local intellectual property be created through dedicated research and development into translational gene therapy and editing. However, the sponsorship needed for a cell or gene therapy product in clinical use is enormous and requires a paradigm shift in fund disbursal and regulatory compliance operations[10]. A major share of the research budget should be supplemented by the Indian and international biotechnology and pharma

industries through collaborative or academic research sponsorship of translational programs. Industry may utilize these technologies, developed for rare diseases, and apply them to more common diseases for long-term financial benefit.

There is an opportunity for stakeholders in India to undertake clinical trials involving locally manufactured CRISPR and associated gene therapy products, such as the treatment for sickle cell anemia. However, in the absence of any such past trials, caution and rigor need to be exercised so that successful therapies can be integrated into national policy for a large number of genetic diseases.

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Published online: 18 January 2024

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Competing interests

The authors declare no competing interests.